IN THE UNITED STATES PATENT AND TRADEMARK OFFICE


In Re Application of: Teruaki SAKINE, et al

Application No.: 09/214,848

Filed: January 14, 1999

For: REMEDIES/PREVENTIVES FOR VIRAL INFECTION

Art Unit: 1616

Examiner: F. I. CHOI

Washington, D.C.

Atty.'s Docket: SEKINE=1

Date: May 26, 2005

**Confirmation No. 8123**

THE COMMISSIONER OF PATENTS
U.S. Patent and Trademark Office
Customer Service Window
Randolph Building, **Mail Stop AF**
401 Dulany Street
Alexandria, VA 22314

Sir:

Transmitted herewith is a [XX] REPLY TO FINAL ACTION: FURTHER REQUEST FOR RECONSIDERATION in the above-identified application.

[XX] Small Entity Status: Applicant(s) claim small entity status. See 37 C.F.R. §1.27.

[ ] No additional fee is required.

[XX] The fee has been calculated as shown below:

| | (Col. 1) CLAIMS REMAINING AFTER AMENDMENT | | (Col. 2) HIGHEST NO. PREVIOUSLY PAID FOR | (Col. 3) PRESENT EXTRA EQUALS |
|---|---|---|---|---|
| TOTAL | * 24 | MINUS | ** 37 | 0 |
| INDEP. | * 3 | MINUS | *** 3 | 0 |
| FIRST PRESENTATION OF MULTIPLE DEP. CLAIM | | | | |

| SMALL ENTITY RATE | SMALL ENTITY ADDITIONAL FEE | OR | OTHER THAN SMALL ENTITY RATE | OTHER THAN SMALL ENTITY ADDITIONAL FEE |
|---|---|---|---|---|
| x 25 | $ | | x 50 | $ |
| x 100 | $ | | x 200 | $ |
| + 180 | $ | | + 360 | $ |
| ADDITIONAL FEE TOTAL | $ | OR | TOTAL | $ |

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.

** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 20, write "20" in this space.

*** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (total or independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment of the number of claims originally filed.

[XX] Conditional Petition for Extension of Time

If any extension of time for a response is required, applicant requests that this be considered a petition therefor.

[XX] It is hereby petitioned for an extension of time in accordance with 37 CFR 1.136(a). The appropriate fee required by 37 CFR 1.17 is calculated as shown below:

| Small Entity Response Filed Within | | Other Than Small Entity Response Filed Within | |
|---|---|---|---|
| [ ] First | - $ 60.00 | [ ] First | - $ 120.00 |
| [XX] Second | - $ 225.00 | [ ] Second | - $ 450.00 |
| [ ] Third | - $ 510.00 | [ ] Third | - $ 1020.00 |
| [ ] Fourth | - $ 795.00 | [ ] Fourth | - $ 1590.00 |
| Month After Time Period Set | | Month After Time Period Set | |

[ ] Less fees ($_____) already paid for ___ month(s) extension of time on _____.

[ ] Please charge my Deposit Account No. 02-4035 in the amount of $_____.

[XX] Credit Card Payment Form, PTO-2038, is attached, authorizing payment in the amount of $ 225.00

[ ] A check in the amount of $_____ is attached (check no. ).

[XX] The Commissioner is hereby authorized and requested to charge any additional fees which may be required in connection with this application or credit any overpayment to Deposit Account No. 02-4035. This authorization and request is not limited to payment of all fees associated with this communication, including any Extension of Time fee, not covered by check or specific authorization, but is also intended to include all fees for the presentation of extra claims under 37 CFR §1.16 and all patent processing fees under 37 CFR §1.17 throughout the prosecution of the case. This blanket authorization does not include patent issue fees under 37 CFR §1.18.

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

ATTY.'S DOCKET: SEKINE=1

| | | |
|---|---|---|
| In re Application of: | ) | Art Unit: 1616 |
| Teruaki SEKINE | ) | Examiner: F. I. Choi |
| Appln. No.: 09/214,848 | ) | Washington, D.C. |
| Filed: January 14, 1999 | ) | Confirmation No. 8123 |
| For: REMEDIES/PREVENTIVES FOR VIRAL INFECTIONS,... | ) | May 26, 2005 |

**REPLY TO FINAL ACTION: FURTHER REQUEST FOR RECONSIDERATION**

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window
Randolph Building, Mail Stop **AF**
401 Dulany Street
Alexandria, VA 22314

Sir:

This will further Reply to the Final Office Action mailed July 27, 2004. Attached is a request for two-months' extension of time and the required two-months' late fee.

The undersigned newly appointed attorney of record requests that:

(1) the PTO change its records to reflect the new attorney Docket which is SEKINE=1;

(2) the PTO address all future correspondence to



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624 9th Street, N.W.
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The Final Action of July 27, 2004, has been carefully studied. Claims 12-27, 29 and 31-37 currently appear in this application. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. As no amendments are presented herewith, applicant respectfully requests entry of the present Reply, as well as favorable reconsideration and formal allowance of the claims.

The present invention is directed to a method and composition for treating herpes group viral infections. The composition comprises an activated autologous lymphocyte effective against and specific for the herpes group viral infection being treated. Lymphocytes are obtained from a herpes group virally infected patient, or a patient who is immunodeficient or immunosuppressed as a result of a herpes group viral infection, and these lymphocytes are treated to be effective against the specific herpes group viral infection being treated.

The patient's lymphocytes are cultured in a culture medium comprising anti-CD3 antibodies in a solid phase and interleukin-2 so as to proliferate and activate the lymphocytes *in vitro*. This composition is then administered to the patient.

Claims 12-27, 29 and 31-37 stand rejected under 35 U.S.C. 103(a) as obvious from Ochoa et al, 5,443,983 (Ochoa '983) in view of Rosenberg 4,690,915 (Rosenberg) and Melder et al (Melder), and further in view of the acknowledged prior art and Wallace et al (Wallace) or the acknowledged prior art and Rooney et al (Rooney), each in further view of Babbitt et al (Babbitt) and Ochoa et al 5,296,353 (Ochoa '353). As understood there are two different rejections each based on a combination of seven (7) different "references". These rejections are respectfully traversed.

The Examiner's position, as understood, is that applicant acknowledges that T-cells are involved in cellular immunity against cancer and viruses, and that lymphocytes, including T-cells, can be activated and stimulated by IL-2, with or without CD3 antibodies. Wallace and Rooney are said to teach that T-cells activated with IL-2 are effective against EBV. Babbitt is said to teach activation of autologous T-lymphocytes with OKT3 and cytokines, including IL-2, for treating viruses such as herpes simplex and Epstein-Barr viruses. Ochoa '353 is said to teach activation of autologous T-lymphocytes with anti-CD3 nod cytokines.

This rejection is respectfully traversed in part because the PTO has demonstrated no motivation to combine the cited references to arrive at the claims presently at issue,

*i.e.*, no valid *prima facie* case of obviousness has been established as required by MPEP §§ 2143 and 2143.01.

Ochoa '983 discloses culturing lymphocytes in the presence of IL-02 and anti-CD3. However, there is no indication that the cells cultured are autologous cells, and there is no disclosure that the lymphocytes are specific for herpes group viral infections. The examples given are for cytotoxicity and antitumor activity. In Ochoa '983, lymphocytes collected from twin brothers who are AIDS patients are cultured and then injected into AIDS patients, confirming only that the patients showed no adverse side effects. Anti-viral activity was not confirmed. This does not lead one of ordinary skill in the art toward applicant's invention.

Rosenberg discloses a method for treating cancer by administering lymphokine activated killer cells (LAK) in conjunction with IL-2. This disclosure is limited to treating cancer, and the IL-2 is administered to the patient, not used to treat the cells.

Melder discloses a technique for producing highly enriched cultures of natural killer cells. Natural killer cells are activated with IL-2, and these cells may be useful in treating HIV infection.

Wallace and Rooney merely treat T-cells with IL-2; there is no disclosure of using anti-CD3 to produce activated

cells. Wallace et al did not treat patients with the activated cells, but only compared the activated cells to cells from patients infected with Epstein-Barr virus. Rooney et al prepared EBV-specific cytotoxic T-lymphocytes from donor cells, not from autologous cells.

Babbitt discloses a process for activating patient-derived mononuclear cells by exposing the cells *in vitro* to substances to generate immunoreactive cells. In this case, soluble OKT3 is used to culture PBMC (peripheral blood mononuclear cells) with OKT3 and a nonspecific lymphocyte activator to produce an OKT3-derived culture supernatant (T3CS). The T3CS is removed from the sample of patient-derived mononuclear cells and the concentration of OKT3 cells in the T3C is determined. If required, the T3CS is supplemented with additional OKT3 to achieve a concentration of at least 0.1 ng/ml. A second sample of cells is obtained from the patient, and this second sample is contacted with the previously-generated T3CS for a period of time sufficient to yield a population of immunoreactive cells. In Babbitt, the culture supernatant is used to produce immunoreactive cells. The immunoreactive cells require further exposure to an immune stimulant, such as an antigen, target cell, virus-infected cell, etc.

Ochoa '353 is concerned with identifying patients who are candidates for adoptive immunotherapy and for identifying agents that cause or reverse immunosuppression. The immunosuppression can be circumvented by recombinant methods, which is not at all the same as the use of activated autologous cells of the present invention.

One skilled in the art reading the cited references would not arrive at the present invention because there is no motivation provided in the prior art to combine the references to achieve the autologous herpes group-specific activated T-lymphocytes of the present invention, and to treat patients with these activated cells.

Ochoa '983 discloses a similar type of culturing as claimed herein, but there is no indication that the cells cultured are autologous cells, nor that the lymphocytes are specific for herpes group viral infections. Since the patient to be treated is immunosuppressed, one could assume that the patient's cells are not able to be activated sufficiently to fight off the viral infection, and that donor cells must be used. None of the cited references addresses this immunosuppression, and it should be noted that one skilled in the art would be reluctant to activate immunosuppressed autologous cells.

Rosenberg treats cancer with a combination of activated killer cells and IL-2, rather than producing activated cells with IL-2. There is nothing in Rosenberg in combination with Ochoa '983 that would lead one skilled in the art to produce autologous cells cultured with anti-CD3 and IL-2 to treat specific herpes viral infections.

Melder uses cells activated by IL-2 to treat cancer, which adds nothing to the disclosures of Ochoa et al '983 and Rosenberg. Even if the proposed combination were obvious (contrary to applicant's position), the combination would not lead to the present invention.

Wallace only treats cells with IL-2 to activate the cells, and there is no indication that these cells can be used to treat patients. Rooney also only shows use of IL-2 to produce activated cells, but these cells were lymphocytes from donor cells, not from autologous cells. The disclosure of treating cells with IL-2 adds nothing to the references cited above to lead one skilled in the art to treat autologous cells for specific treatment of herpes viral infections.

Babbitt discloses generating immunoreactive cells by a two-step process, using a culture supernatant to produce activated cells. This would not lead one skilled in the art to prepare immunoreactive cells by a one-step process.

Ochoa '353 discloses methods for identifying patients who are candidates for adoptive immunotherapy, but teach that immunosuppression can be circumvented by recombinant methods, not by injecting autologous activated cells into a patient. The present invention is for activating cells and then treating patients with specific herpes viral infections. A method for identifying patients who are candidates for adoptive immunotherapy, without a disclosure of the specific herpes viral infection treated, adds nothing to the above-noted disclosure.

There is nothing in any combination of these references that would lead one skilled in the art to use the specific method of the present invention for activating autologous cells for specific herpes group viral infections and for treating patients with these autologous cells.

As the Federal Circuit stated in *In re Lee*, 61 USPQ2d 1430 (January 18, 2002, Fed. Cir.), "As applied to the determination of patentability *vel non*, when the issue is obviousness, 'it is fundamental that rejections under 35 U.S.C. 103 must be based on evidence comprehended by the language of that section.' *In re Grasselli*, 53 USPQ2d 1769, 1774 (Fed. Cir. 2000)... When patentability turns on the question of obviousness, the search for an analysis of the prior art includes evidence relevant to the finding of whether

there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness *See, e.g., McGinley v. Franklin Sports, Inc*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001), 'the central question is whether there is a reason to combine [the] references,' a question of fact drawing on the *Graham* factors."

'The factual inquiry whether to combine references must be thorough and searching' *Id.* This precedent has been reinforced in myriad decisions, and cannot be dispensed with, *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000), ('a showing of a suggestion, teaching, or motivation to combine the prior art references is an "essential component of an obviousness holding"'), quoting *C. R. Bard, Inc. v. M3 Systems, Inc.* 48 USPQ2d (Fed. Cir. 1998). The Court went on to quote *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999), "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."

There is a requirement for specificity in combining references, *See, In re Kotzab*, 55 USPQ2d 13134, 1317 (Fed. Cir. 2002), "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed

invention, would have selected these components for combination in the manner claimed."

In the present case, the PTO has shown no motivation to combine the multitude of cited references to arrive at the particular invention claimed herein. Withdrawal of the rejections is in order and is respectfully requested.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is therefore earnestly solicited.

Respectfully submitted,

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